Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 297-357 are pending and under consideration in the application, with claims 297, 309, 320, 332 and 343 being the independent claims. Claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296 have been canceled without prejudice or disclaimer of the subject matter therein. New claims 297-357 have been added. Support for the new claims can be found in the previously presented claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296, and at paragraphs [0019], [0026], [0089] and [0092] of the published application. These changes are believed to introduce new matter, and their entry is respectfully requested.

The specification has been amended to correct a typographical error in the sequence identifiers listed in paragraph [0070]. Support for this amendment can be found in paragraph [0101] of the specification and in the wording of paragraph [0070] itself that indicates there are three codon-optimized sequences of SEQ ID NO: 12 obtained by the procedure in the same paragraph. Accordingly, these changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

35 U.S.C. § 112, first paragraph (scope of enablement)

The Examiner has rejected claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296 under 35 U.S.C. § 112, first paragraph. *See* Office Action, hereinafter "OA" at pages 3-12. The Examiner asserts that the specification while "being enabling to reduce the severity of anthrax infection" in a mammal, does not reasonably provide enablement for a method of "prophylactic vaccination to prevent or protect against anthrax infection." OA at pages 3. Specifically, the Examiner asserts that "[t]he aspects considered broad are: methods of prophylactically vaccinate [sic] a vertebrate against anthrax infection by eliciting a prophylactic effective immune response thereby protecting said vertebrate against anthrax infection." OA at page 4. Claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296 have been canceled. Insofar that the rejection applies to the currently pending claims 297-357, Applicant respectfully traverses this rejection.

Applicant requests clarification on the following issue, claims 231, 232, 235, 237-244, 261, 262, 265, 267-274, 294 and 296 directed to methods of reducing the severity of anthrax infection are included in the present rejection. OA at page 3. New claims 309-319 and 332-342 are directed to a method of reducing the severity of anthrax infection. The embodiment of reducing the severity of anthrax infection is specifically indicated by the Examiner as being enabled. OA at page 3. Applicant requests clarification as to why these claims are included in the present rejection, when the

Examiner specifically indicated that the claims are enabled to reduce the severity of anthrax infection,

Claims 275, 276, 279, 281-292 directed to a composition and are included in this scope of enablement rejection. OA at page 3. New claims 343-357 are directed to a composition. The composition is directed to a carrier, a lipid selected from GAP-DMORIE, DMRIE and combination thereof, a co-lipid and an isolated polynucleotide encoding a polypeptide identical to amino acids 30-764 of SEQ ID NO: 4 wherein the amino acids Ser-Arg-Lys-Lys-Arg Ser at position 192-197 of SEQ ID NO: 4 have been deleted. The Examiner asserts that the claims are analyzed for their intended use. The Examiner is reminded that it is generally considered improper to read limitations contained in the specification into the claims. *See* MPEP 2173.05(q) citing *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969) and *In re Winkhaus*, 527 F.2d 637, 188 USPQ 129 (CCPA 1975). Applicant requests clarification as to the inclusion of the composition claims with this scope of enablement rejection.

The Examiner's argument

The Examiner asserts there is enablement in the specification for the limitation "to reduce the severity of anthrax" but not sufficient enablement for a method of "prophylactic vaccination to prevent or protect against anthrax infection." OA at page 3. Examiner asserts that "[t]he aspects considered broad are: methods of prophylactically vaccinate [sic] a vertebrate against anthrax infection by eliciting a prophylactic effective immune response thereby protecting said vertebrate against anthrax infection." OA at page 4. Without any documentation the Examiner alleges that developing the "desired immune response for sustained period to prophylactically vaccinate to prevent disease

such as anthrax remains unpredictable and inefficient in humans." OA at page 6. The Examiner asserts that unpredictability in the art may provide reasonable doubt as to the enablement of the entire scope of the claim citing *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991), *In re Goodman* 29 USPQ2d 2010 (CA FC 1993) and *In re Vaeck*, 20 USPQ2d 1438 (CA FC) in support. The Examiner cites four additional references in support of the assertion that the art is unpredictable. *See* OA at pages 6-10.

The Examiner takes the position that "the specification does not provide any evidence that codon optimized polynucleotide could be delivered to confer immunity resulting in protection against any anthrax infection commensurate with the full scope of the claims in any vertebrate" OA at page 7. The Examiner asserts, "neither the specification nor the art provide adequate guidance to support that a method of generating effective immune response seen in mice or rabbit could be extrapolated to same level of antibody response in human." OA at page 9. "[A] regime of dose scheduling as disclosed from small animal and primate would not be efficacious to confer immunity in humans," citing Leppla *et al.* (J. Clin. Invest. 2002, 110:141-144) in support of this assertion. OA at page 9. The Examiner asserts that "[t]he guidance provided by the specification to fails overcome the art recognized unpredictability of DNA vaccine to elicit immune response in larger mammal for sustained period of time." OA at page 10. Applicant respectfully traverses this rejection.

The legal standard

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed.

Cir. 1988). The captioned application has provided working examples in which three species of animals have been immunized with the claimed DNA based vaccine and all three species have mounted an immune response to protective antigen (hereinafter "PA"), using the PA encoding DNA that is human codon optimized. In challenge experiments all animals that were given the DNA based vaccine survived while all control animals died. *See* Examples 12, 13 and 16. Subjecting rabbits to an aerosolized anthrax spore challenge is "the gold standard for anthrax vaccine efficiency because it exposes the animal to the agent and expected mode of delivery anticipated in the event of a bioterrorist attack." Hermanson, *et al.* Proc. Natl. Acad. Sci. 101:13601-13606 (2004), previously submitted on IDS submitted August 26, 2006, *see* discussion. Because the animals survived the challenge experiments, in a model system determined to be the closest to human infection, Applicant asserts that the captioned application is enabled for methods of prophylactically vaccinating a vertebrate against anthrax infection.

The Examiner must provide reasons for the assertion that the disclosure not enabled and unbelievable. *In re Bowen*, 492 F.2d 859, 862-63 (CCPA 1974). Patent law only requires a showing that "reasonable correlation" exists between the scope of the claims and the scope of enablement. As stated in the M.P.E.P. § 2164.02, "'correlation' as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless the Examiner has evidence that the model does not correlate. *In re Brana*, 51 F.3d 1560, (Fed. Cir. 1995), at 1566. Here the specification has provided working examples in three

animal models. These animal models are well established and accepted correlates of protective immunity in humans.

The first step in an enablement analysis requires the Examiner to construe the claim. As stated in the MPEP § 2111, "the broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach." *In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999). The invention in *Cortright* was directed to methods of treating baldness, such a method in the past was considered an inherently unbelievable undertaking. However, treatments of baldness in the interim have gained acceptance. The specification in *Cortright* had five examples of subjects that used the product and experienced varying degrees of improvement. The Court found that this was a sufficiently enabling disclosure for methods directed to treating baldness. Similarly, the area in the art of DNA vaccination is such that there are currently several phase I and phase II human vaccine trials underway.

The Examiner is reminded that mere breadth of a claim does not make a claim not enabled or indefinite as long as the scope of the subject matter that is embraced is clear. *In re Miller*, 441 F.2d 689 (CCPA 1971). *See* MPEP 2173.04.) Additionally, it is permissible for claims to encompass inoperative embodiments. *See* MPEP 2164.08(b). The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those

embodiments that were operable. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976).

Although, unpredictability in the art may provide reasonable doubt as to the enablement of the entire scope of the claim, the specification itself may contain sufficient support for the full scope even in an unpredictable art. *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991), *In re Goodman* 29 USPQ2d 2010 (CA FC 1993) and *In re Vaeck*, 20 USPQ2d 1438 (CA FC). "We do not imply that patent applicants in art areas currently denominated as 'unpredictable' must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Vaeck, at 1445, citing In re Angstadt, 190 USPQ 214, 218 (CCPA 1976).* Thus, scope of enablement can be overcome with the proper disclosure even if the art is considered unpredictable.

The disclosure of the specification

The present application has provided working examples in which three species of animals (mouse, rabbit and monkey) have been immunized with the claimed DNA based vaccine and all three species have mounted an immune response to protective antigen (hereinafter "PA"), using the PA encoding DNA that is human codon optimized. *See* Examples 11-16. Subjecting rabbits to an aerosolized anthrax spore challenge is "the gold standard for anthrax vaccine efficiency because it exposes the animal to the agent and expected mode of delivery anticipated in the event of a bioterrorist attack." Hermanson, *et al.* Proc. Natl. Acad. Sci. 101:13601-13606 (2004), *see* discussion. In challenge experiments, using the rabbit spore challenge model all animals that were

given the DNA based vaccine survived while all control animals died. *See* Examples 12, 13 and 16. The specification provides that any mode of administration can be used so long as the mode results in the expression of the desired *B. anthracis* peptide or protein. *See* published application paragraph [0133]. Measuring the level of protein expression in a given tissue after administration of the composition is well within the skill of the ordinary artisan. Determining the precise amount, number of doses, and timing of doses are also within the skill of the ordinary artisan. An ordinary artisan in the field vaccination will be the attending physician or veterinarian. *See* published application paragraph [0134]. The specification also provides a number of *in vitro* assays, which are well established and art recognized correlates for challenge experiments. *See* published application paragraph [0161]. These *in vitro* assays allow the ordinary artisan to monitor the immune response in the inoculated vertebrate and determine whether the vertebrate will need to undergo additional inoculations in order to be protected from the pathogen. Thus, the specification has provided a clear road map to allow the ordinary artisan in the field of vaccinology to practice the invention without undue experimentation. The Examiner is reminded that an enabling disclosure allows for some experimentation even in large amounts as long as it is not undue. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The facts in *Singh*, *Goodman* and *Vaeck*, cited by the Examiner, differ significantly from the facts in the present application. In *Singh* the specification only provided a single example for the secretion of a mature protein, at the same time the specification itself provided reasons to doubt the predictability in this area of the art. In *Goodman* the specification provided a single working example. *Goodman's* own

publications showed that this area in the art would require extensive experimentation, thus, leading the Court to conclude that the specification is not enabled for the full scope. In *Vaeck* the specification also only provided a single working example. In contrast, the present specification provides working examples in mice, rabbit and monkey, models that show the instantly claimed vaccine formulation induces an immune response in each animal. *See* published application Examples 11-16. Rabbits are an art-recognized model for studying anthrax pathogenesis and therapeutic regimes. *See* Zaucha *et al.* Arch. Pathol. Lab. Med. 122:982-992 (1998), submitted herewith on an IDS form, see conclusion. The inhalation spore challenge is the gold standard for testing anthrax infection. *See* Hermanson, *et al.* Proc. Natl. Acad. Sci. 101:13601-13606 (2004), *see* discussion. Applicant has shown that that the vaccine provides complete protection in the animals when challenged with a lethal dose of inhaled anthrax. *See* published application paragraphs [0239-0248]. Here, the specification has exemplified the prevention of anthrax infection in three animals models: mouse, rabbit and monkey. Rabbits are an art-recognized model for studying anthrax pathogenesis and therapeutic regimes. The specification has enabled the delivery of a codon optimized DNA to a vertebrate to confer protective immunity against anthrax infection. Thus, contrary to the facts in *Singh*, *Goodman* and *Vaeck* the present specification solidly enables the full scope of the claims.

The Examiner alleges that the art of DNA vaccination is unpredictable citing Galloway and Baillie (Expert Opin, Biol. Ther. 2004, 4:1661-1667), *Van Drunen Little - van den Hurk (Immunology Reviews 2004,* 119: 113-125), Rosenberg (Human Gene Therapy 2003, 14-709-714) and Leppla *et al.* (J. Clin. Invest. 2002, 110:141-144). The

present application provides documented evidence that the animal experiments are well established and well accepted correlates for protective immunity in humans. *See* published application paragraph [0161]. None of the evidence or arguments set forth by the Examiner even comes close providing that these established immune correlates are "unbelievable." Whether or not the Examiner has successfully demonstrated "unpredictability" based on these references this is not controlling, because the present specification has more than enabled the claimed invention whether or not the art is "unpredictable." The Examiner is reminded that just because the area in the art may be unpredictable does not necessarily mean that Applicant is limited to only those species disclosed in the specification. *See In re Vaeck, at 1445, citing In re Angstadt, 190 USPQ 214, 218 (CCPA 1976).*

The Examiner has not provided any reason to doubt the truth of the statements concerning the prophylactic effect using the claimed methods and composition as disclosed in the specification or the acceptance of certain animal model, especially rabbit inhalation challenge model, as correlating to protective immunity in humans. *See In re Cortright*, 165 F.3d 1353, at 1357. Even if the idea of prophylactic anthrax vaccination could have been considered unbelievable at one time, the use of the commercially available AVA vaccine without failure for over 30 years provides evidence that methods of prophylactically preventing anthrax infection are enabled. There are several art recognized *in vitro* assays, which are well accepted by those of ordinary skill in the art to be correlates for challenge experiments. *See,* e.g., Reuveny, S. *et al.* Infect. Immun. 69:2888-2893 (2001); Kobiler, D. *et al.* Infect. Immun. 70:544-560 (2002); Pitt, M. L. *et al.* Vaccine 19:4768-4773 (2001); and Park, S., and Leppla, S. H. Protein Expr. Purif.

18:293-302 (2000). These referenced are cited on the IDS and are incorporated into the present specification in their entirety. *See* paragraph [0161] of the published application. Additionally, the present specification uses the "gold standard" animal challenge model, the rabbit, for studying anthrax infection and prevention and demonstrate clear protective immunity. *See* Zaucha *et al.* Arch. Pathol. Lab. Med. 122:982-992 (1998) and Hermanson, *et al.* Proc. Natl. Acad. Sci. 101:13601-13606 (2004). The present specification has established that rabbits vaccinated with the presently claimed DNA composition produce a protective immune response against lethal inhalation challenge using anthrax spores. Thus, for the reasons given above, Applicant submits that the scope of the present claims is commensurate in scope with the enablement provided in the present specification. The considerations raised by the Examiner either are resolved by the teachings in the specification or would have required only routine experimentation by one of skill in the art to practice the claimed invention. Accordingly, Applicant requests reconsideration and withdrawal of the scope of enablement rejection in view of the amendments to the claims and the remarks herein.

The Examiner asserts, "neither the specification nor the art provide adequate guidance to support that a method of generating effective immune response seen in mice or rabbit could be extrapolated to same level of antibody response in human." OA at page 9. "[A] regime of dose scheduling as disclosed from small animal and primate would not be efficacious to confer immunity in humans," citing Leppla *et al.* (J. Clin. Invest. 2002, 110:141-144) in support of this assertion. OA at page 9. Applicant respectfully notes that despite this belief a person of ordinary skill in the art reading the specification could easily scale this immunization protocol based in common knowledge

and the road map presented, e.g., in the specification at paragraph [0133] of the published application.

The Examiner asserts that "[t]he guidance provided by the specification to fails overcome the art recognized unpredictability of DNA vaccine to elicit immune response in larger mammal for sustained period of time." OA at page 10. Applicant respectfully reminds the Examiner that the proper standard for compliance with enablement, is not absolute predictability but objective enablement; evidence need not be conclusive but merely convincing. Indeed, the evidence provided in the specification is convincing, e.g., to the FDA. *See infra.* Accordingly, Applicant submits that the compelling animal data presented in the specification is sufficiently convincing that one of ordinary skill in the art would not doubt the feasibility of the claimed invention. Moreover, the *in vivo* successes documented in the Examples of the instant specification, e.g. Examples 10-13, clearly outweigh any speculative allegations of unpredictability asserted by the Examiner.

Furthermore, contrary to the Examiners assertion, DNA immunization in large animals (bovine) has been shown to be effective, for example against bovine herpesvirus-1 in cattle. *See Van Drunen Little - van den Hurk, Immunology Reviews 2004,* 119: 113-125, at page 115, col. 2, last paragraph. Here, a plasmid encoding bovine herpesvirus-1 gD protein was administered intervaginally. This route of administration stimulated the IgG and IgA production in the nasal and vaginal membranes. Intranasal virus challenge showed that the magnitude of the infection was reduced as observed by the reduction in weight loss and the reduced virus shedding. *See*

Id. page 115, col. 2, last paragraph. Thus, contrary to the Examiner's assertion, DNA vaccines have been shown to be effective large vertebrates.

According to the Examiner's apparent view of the scope of enablement requirement, an Applicant would have to submit conclusive data from human clinical trials in order to adequately enable a method of treatment applicable to humans. Clearly exposing humans to anthrax in human clinical trials is highly unethical and is not required by the FDA for approval of an anthrax vaccine. *See* 67 Fed. Reg. 37989, May 31, 2002, previously provided in the response of September 11, 2006. In addition, this is clearly in conflict with the statute, the rules and the guidelines of the M.P.E.P. Specifically, under the current case law, clinical efficacy is not required to show that a therapeutic process is operable. As stated in M.P.E.P. § 2107.01, the "courts have found utility for therapeutic inventions, despite the fact that an applicant is at a very early stage in the development of a therapeutic regimen" or that a therapeutic treatment regimen is not at a stage where it is ready to be practiced on humans. *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

It is not within the province of the USPTO to require proof of efficacy in animals, let alone humans, to grant a patent including claims to therapeutic methods. The FDA will accept evidence from animals studies to provide substantial evidence of the effectiveness of products, when human efficacy studies are not feasible. For the FDA approval purposes it is sufficient to establish the effect in either more than one animal, or in a single well-characterized animal model that has been shown to predict the human response. *See* 67 Fed. Reg. 37989, May 31, 2002, previously provided in the response of

September 11, 2006. The PTO guidelines do not require proof of efficacy, in fact are explicit on this point: "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders." M.P.E.P. § 2107.03. The guidelines further state that "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law, and in quoting *In re Brana*, *supra*, that "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws". *Id.* In fact, all that is required by the patent laws is that a "reasonable correlation" exists between the scope of the claims and the scope of enablement. Citing to M.P.E.P. § 2164.02, "'correlation' as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." If a particular model is recognized as correlating to a specific condition, as is the rabbit model as exemplified in Zaucha *et al.*, then it should be accepted as such unless the Examiner has evidence that the model does not correlate. *In re Brana*, *supra* at 1566. Since the initial burden is on the Examiner to give reasons for lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. As stated in *Cross v. Iizuka*, *supra*, at 1050, a rigorous or an invariable exact correlation is not required.

The references cited by the Examiner and arguments set forth in view of those references do not cast doubt on the feasibility of the claimed invention in light of the data presented in the specification. Indeed, the captioned application describes various in *vitro* assays known in the art which are well accepted by those of skill in the art to

correlate to *in vivo* anthrax challenge experiments, e.g., at paragraph [0155] of the specification. The specification also describes data for various claimed vaccine compositions in three different animal models. See Examples 10-13 and 15. Furthermore, the captioned application contains data showing that DNA vaccines containing codon-optimized polynucleotides encoding anthrax antigens can provide protective immunity in rabbit using inhalation challenge considered the "gold standard," and measured by toxin neutralization antibody titers in mice and non-human primates. *See* Examples 11-16. Finally, post-filing art, co-authored by the inventor of the captioned application, reports that the rabbit studies described herein resulted in product selection, pre-clinical safety studies, and a U.S. FDA Investigational New Drug allowance. "A cationic lipid-formulated plasmid DNA vaccine confers sustained antibody-mediated protection against aerosolized anthrax spores." *See* Hermanson *et al.* Proc. Natl. Acad. Sci. 101:13601-13606, 1306 (2004), IDS of August 26, 2005. Applicant asserts that a clearly recognized and accepted correlation thus exists between the data provided in the captioned application and the claimed methods.

Thus, given the explicit disclosure of specific *in vivo* working examples, using models that reasonably correlate to mammals, as noted in paragraph [0161] of the published application, Applicant respectfully submits that one skilled in the art would be able to make and use the claimed invention without undue experimentation. Applicant respectfully requests reconsideration and withdrawal of this rejection.

35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296 under 35 U.S.C. § 112, second paragraph. OA at pages 11-12. Solely to advance prosecution and not in acquiescence of any of the Examiner's assertions, Applicant have canceled claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296 and added new claims 297-357 that recite "wherein the amino acids Ser-Arg-Lys-Lys-Arg-Ser at position 192 to 197 of SEQ ID NO:4 have been deleted." As such, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 215, 216, 219, 222-228, 231, 232, 235, 238-243, 249, 275, 276, 279, 282-290 and 293 under 35 U.S.C. § 103(a) as being unpatentable over Lee *et al.* (U.S. Pat. App. No. 2004/0009945, publication date January 15, 2004, effective filing date July 10, 1998, hereinafter "Lee"); Klimpel (Proc. Nat. Acad. Sci U.S.A. 1992, Vol. 89, No. 21, pages 10277-10281); Singh *et al.* (J. Biol. Chem. 1994, Vol. 269, No. 46, pages 29039-29046, hereinafter "Singh"), Nagata *et al.* (Biochemical Biophysical Research Comm. 1999, Vol. 261, No. 2, pages 445-451; hereinafter "Nagata") and Hartikka *et al.* (Vaccine 2001, Vol. 19, pages 1911-1923; hereinafter "Hartikka"). OA at pages 12-16. More specifically, the Examiner asserts that Lee emphasizes that it would be routine "to optimize codon expression for a particular host." OA at page 13. The Examiner further asserts that the reference also suggest that "Lee had already disclosed that it would be routine for one skilled in the art to generate

the degenerate variants, for instance, to optimize codon expression for a particular host." OA at page 15. The Examiner asserts that Klimpel teaches "cleavage by a cellular protease at sequence Arg-Lys-Lys-Arg, normally follows binding of protective antigen (PA) to a cell surface receptor." OA at page 14. The Examiner asserts that Singh cites Klimpel "to describe that introduction of mutations at this site in combination with deletion of the activation site at residues 164-167 for furin cleavage site described by Klimpel produces an altered PA that may have several advantages for use in anthrax vaccine." OA at page 14. According to the Examiner Nagata teach the use of the *Homo sapiens* codon optimization tables. OA at page 15. Hartikka teach the use of cationic lipid, for example GAP-DMORIE : DPyPE, to elicit an immune response. OA at page 15. Claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296 have been canceled. Insofar that the rejection applies to the currently pending claims 297-319 and 343-357, Applicant respectfully traverses this rejection.

The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The Office has recently published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc. Fed.* Reg. Vol. 72, pp. 57526 to 57535 (October 10, 2007), hereinafter "the Examination Guidelines." Seven rationales are suggested by which obviousness may be found, e.g.,

by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were *predictable*. *Id.*, e.g., at 57529

The Examiner impermissibly rejects the claims as being obvious over the cited art while at the same time asserting that the art in the area of DNA vaccination in general was unpredictable, and was especially unpredictable in reference to anthrax vaccination. *See* OA at pages 3-11. Art that is deemed unpredictable cannot be properly combined to reject a claim under 35 U.S.C. § 103(a) as being obvious, because in order to establish a *prima facie* case of obviousness requires a factual showing that the combination is *predictable.*

Initially, in order to support a *prima facie* case of obviousness, the prior art must suggest making the specific molecular modifications necessary to achieve the claimed invention. See *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984) ("[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). That is, simply because "one can conceive a general process in advance for preparing an undefined compound [*e.g.*, a codon optimized polynucleotide encoding the protective antigen of *B. anthracis*] does not mean that a claimed specific compound. *See In re Deuel* at 1559. Specifically, a polynucleotide selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25 specifically recited in independent claims 297, 309, 320, 332 and 343 was not precisely envisioned in the prior art and therefore the composition cannot be obvious. Thus, in order for the cited

reference to be suitable as primary references upon which to base a *prima facie* case of obviousness, it must be *predictable* that the artisan would arrive at the specifically claimed sequences selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25 as claimed. Especially in view of the numerous potential polynucleotides which could encode for SEQ ID NO:4 with the furin cleavage site deleted and the numerous potential ways to codon optimize the polynucleotides it would not be predictable to arrive at sequence SEQ ID NO: 23, SEQ ID NO: 24 or SEQ ID NO: 25 as presently claimed. Therefore, the cited references taken together are seriously deficient (particularly in view of the holding in *Deuel*), and cannot support a *prima facie* case of obviousness.

In a recent post KSR Federal Circuit decision the Court reiterated that the requirements for presenting a *prima facie* case of obviousness involving structurally similar compounds is well settled. A *prima facie* case obviousness involving structurally similar compounds requires a showing that there is adequate support in the prior art for the changing the structure of a compound. *See Takeda Chemical Industries v. Alphapharm*, 492 F.3d 1350, at 1356 (2007), citing *In re Grabiak*, 769 F.2d 729, at 731-732 (Fed. Cir. 1985). "Normally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." *Takeda* 492 F.3d at 1356 citing *In re Deuel*, 51 F.3d 1552, at 1558 (Fed.Cir.1995). There is additional requirement that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed.Cir.1992); *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990) ; *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985); *In re Lalu*,

747 F.2d 703 (Fed.Cir.1984)). The court held that in "cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a *prima facie* case of obviousness of a new claimed compound." *Takeda,* 492 F.3d at 1357. Thus, the holding in *Takeda* provides that a *prima facie* case of obviousness requires the identification of a lead compound in the references followed by a clear articulation of the reasons why the artisan would change the compound in a particular way.

Independent claims 297, 309, 320, 332 and 343 are directed to a composition or a method of prophylactically vaccinating a vertebrate or a method of reducing the severity of anthrax infection in a vertebrate "comprising administering to a vertebrate in need thereof a composition comprising a carrier, a lipid GAP-DMORIE, a co-lipid and an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide identical to amino acids 30 to 764 of SEQ ID NO:4, wherein the amino acids Ser-Arg-Lys-Lys-Arg-Ser at position 192 to 197 of SEQ ID NO:4 have been deleted . . . " Applicant asserts that Lee does not teach or suggest the administration of the specifically claimed polynucleotides selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25, as set forth in claims 297, 309, 320, 332 and 343 in combination with the lipid GAP-DMORIE and a co-lipid nor does Lee suggest or disclose the specific codon optimized sequences as recited in the claims.

Lee used VEE replicon particles (VRP) containing the gene for PA to inoculate mice. According to the Examiner's assessment in the enablement rejection, there was unpredictability in the art regarding extrapolating the generation of an effective immune

response observed in a mouse to a large vertebrate, including a human.[1] *See* OA at page 9. Lee only inoculated a single animal model, mice. *See* Lee paragraph [0043]. Furthermore, Lee did not test the effectiveness of the immunization protocol using an inhalation challenge protocol. Instead, Lee challenged the mice with a subcutaneous dose of *B. anthracis* Sterne strain. *See* Lee at paragraph [0046]. It is important to note that the *B. anthracis* Sterne strain is attenuated in some animals, in other words this strain is not lethal in all animals. *See* Lee at paragraph [0048]. The results obtained with the *B. anthracis* Sterne strain, therefore, cannot be extrapolated to protection against lethal anthrax challenge in other vertebrates, let alone human beings. Thus, unlike the present application, the results in Lee cannot predictably be expanded to encompass vertebrates, as claimed in the present application. Additionally, there is no suggestion to remove the furin cleavage site found in the reference of Lee.

Lee does not disclose SEQ ID NO: 4 with the furin cleavage site deleted. The furin cleavage site is made up of the amino acid sequence "SRKKRS" (corresponding to amino acids 192-197 of SEQ ID NO:4). The reference does not disclose a TPA-PA, full-length protective antigen, with a deleted the furin cleavage site. Furthermore, Lee does not suggest the deletion of the furin cleavage site. Thus, the reference does not teach or suggest a full-length PA antigen with the furin cleavage site deleted as required by the present claims. Thus, the reference does not suggest a composition, let alone a method "comprising administering to a vertebrate in need thereof a composition comprising a carrier, a lipid GAP-DMORIE, a co-lipid and an isolated polynucleotide" comprising a

[1] As noted *supra*, Applicant's disclosure of protective immunity in three animal models that are well established and accepted immune correlates for protective immune responses in humans overcoming any allegations of lack of enablement even in view of any prior "unpredictability."

polynucleotide selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25 from which the nucleic acids corresponding to the furin cleavage cite have been deleted.

Klimpel teach that anthrax toxin requires that PA be proteolytically activated. Klimpel at page 10280, col. 1. The reference discloses that furin is a protease located at the cell surface that is capable of cleaving the PA at the Arg-Lys-Lys-Arg sequence. The reference made several PA mutant sequences to evaluate the specific residue requirement and determine whether the PA can also be cleaved by trypsin. *See* Klimpel discussion at page 10280, at page 10278, and table 1. "The chance that several different proteases in an infected animal are capable of activating PA has not been ruled out." Klimpel at page 10279, col. 2. The reference does not teach deleting the furin cleavage site or the specifically codon optimized sequences of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25.

Singh teaches that it "has previously been shown that a non-toxic PA mutant in which residues 163-168 are deleted retained immunogenicity and the ability to induce immunity. The minor changes at residues 313-315 in the PA mutants described here would not be expected to significantly reduce immunity to PA." Singh at page 29045, paragraph spanning col. 1-2. Singh deleted the furin cleavage site to prevent degradation during the protein expression and purification process. Singh expressed the protein in *E. coli* (a gram negative bacterium) followed by affinity purification of the protein before injecting the protein into an animal. *See* Singh at page 29040, col. 1, paragraph 4. Singh did not demonstrate that PA with a deleted furin cleavage site will provide protective immunity in a vertebrate, let alone a human. In the prior reference cited by Singh, the

PA with the deleted furin cleavage site was expressed in *Bacillus subtitles* (a gram positive bacterium). *See* Singh at page 29045, paragraph spanning col. 1-2, citing Singh *et al.* J. Biol. Chem., 1989, Vol. 264, No. 32, pages 19103-19107, submitted herewith in an IDS form, hereinafter "Singh2". As in Singh, Singh2 did not actually test the deleted PA product for immunogenicity. The animal data in Singh2 is limited to a rat study in which the rats were injected with PA, LF or combinations thereof. The deleted PA was either injected at the same time as the PA and LF combination or was administered before the PA and LF combination. Another factual distinction, protein expressed and purified from bacteria, even if highly purified, will comprise added components such as lipopolysaccharide (LPS - found in gram negative bacteria) or lipoteichoic acid (LTA - found in gram positive bacteria), both components are known immunostimulatory molecules, which would effect immunogenicity. Thus, a composition comprising a purified protein from a bacterial cell culture would be expected to have , e.g., immuunostimulatory molecules relative to a DNA vaccine. Thus, Singh does not predictably suggest to a person of ordinary skill in the art that a DNA vaccine using the deleted PA protein would protect a vertebrate against a lethal challenge by *B. anthracis*. Singh does not disclose using DNA as an immunogenic composition. Therefore, the reference, which only shows a purified protein isolated from bacteria, lacks a showing that such a polynucleotide could predictably result in protection against lethal challenge by *B. anthracis*. Finally, the reference does not teach the specifically codon optimized sequences of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25.

Hartikka does not cure the deficiencies of Lee, Klimpel and Singh. Hartikka discloses the injection of mice using Vaxfectin formulated with pDNA encoding

influenza nucleoprotein (NP). Hartikka Abstract, page 1911. "The mechanism by which Vaxfectin enhances the antigen-specific antibody response is unclear." Hartikka page 1921, column 1, 2nd paragraph. "Experiments are underway to further characterize the critical features of the Vaxfectin-derived response, and to expand the scope of the application of Vaxfectin adjuvancy for pDNA vaccines to other antigens, tissues, routes of administration and target species." Hartikka page 1921, column 2, last paragraph. Thus, the ordinary artisan after reading Hartikka would not have had an expectation of success in using other antigens because the authors clearly indicate that further studies are needed. Additionally, Hartikka does not teach or suggest the administration of a codon-optimized polynucleotide of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25.

Nagata does not cure the deficiencies of Lee, Klimpel and Singh. Indeed, Nagata discloses the use of a gene encoding amino acid residues 91 to 99 of listeriolysin O (LLO) derived from *Listeria monocytogenes*. The gene was codon optimized for mouse and then used to immunize mice via the gene-gun delivery method. Nagata does not teach or suggest the administration of a codon-optimized polynucleotide of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25 with a deleted furin cleavage site administered to a vertebrate in a composition comprising GAP-DMORIE and a co-lipid as claimed.

As such, the combined references cited by the Examiner do not suggest the claimed methods, and specifically claimed molecular modifications. Therefore, Applicant respectfully requests withdrawal of the rejection as it relates to the currently pending claims.

The Examiner has rejected claims 215, 216, 219, 222-228, 231, 232, 235, 238-243, 249, 275, 276, 279, 282-290 and 293 under 35 U.S.C. § 103(a) as being unpatentable over Lee *et al.* (U.S. Pat. App. No. 2004/0009945, publication date January 15, 2004, effective filing date July 10, 1998, hereinafter "Lee"); Klimpel (Proc. Nat. Acad. Sci U.S.A. 1992, Vol. 89, No. 21, pages 10277-10281); Singh *et al.* (J. Biol. Chem. 1994, Vol. 269, No. 46, pages 29039-29046, hereinafter "Singh"), Nagata *et al.* (Biochemical Biophysical Research Comm. 1999, Vol. 261, No. 2, pages 445-451; hereinafter "Nagata") and San *et al.* (Hum Gene Ther, 1999, Vol. 4, No. 6, pages 781-788; hereinafter "San"). OA at pages 16-18. The Examiner asserts that "it was routine to use plasmid DNA encoding the transgene complexed with a cationic lipid mixture, DMRIE/DOPE for *in vivo* DNA-based immuno therapy." OA at page 17. The Examiner asserts that San discloses the use of DMRIE/DOPE - DNA complexes as "formulations that is well-tolerated *in vivo* and could therefore allow higher dose administration and potentially greater efficacy of gene transfer." OA at page 17. Claims 215, 216, 219, 221-232, 235, 237-246, 249, 251-262, 265, 267-276, 279 and 281-296 have been canceled. Insofar that the rejection applies to the currently pending claims 320-357, Applicant respectfully traverses this rejection.

The deficiencies of Lee, Klimpel, Singh and Nagata have been discussed above. San does not cure the deficiencies of Lee, Klimpel, Singh and Nagata. Specifically, San discloses the use of plasmids in combination with DMRIE/DOPE for the introduction of an HLA-B7 gene under the control of the Rous sarcoma virus terminal repeat sequence. San does not teach or suggest the administration of a codon-optimized polynucleotides

selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25 with a deleted furin cleavage site administered to a vertebrate in a composition comprising DMRIE/DOPE and a co-lipid as presently claimed. As such, the combined references cited by the Examiner do not suggest the claimed methods, and specifically claimed molecular modifications. Therefore, Applicant respectfully requests withdrawal of the rejection as it relates to the currently pending claims.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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